REMARKS

Claims 1-16 are pending in the application. Claims 17-47 were withdrawn pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention. The election was made without traverse in Paper No. 11. Claim 16 has been amended to recite the generic name for the dyes instead of using the trademark name. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the remarks that follow.

REJECTIONS

Rejection of Claim 16 under 35 USC §112, second paragraph.

The Examiner has rejected claim 16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserts Applicants are claiming trademarked labels for which Applicant must claim the compound and not the trademarked compound. Applicants have amended claim 16 to recite the known chemical name of the previously recited trademarks at the time the invention was filed. No new matter is believed to be introduced by this amendment.

Quantum Red™ has been deleted. Texas Red maleimide is disclosed in TABLE 1, and the term Texas Red ™ is replaced by its known IUPAC name--(9-(2(or4)-(N-(2-maleimdylethyl)-sulfonamidyl)-4(or 2)-sulfophenyl)-2,3,6,7,12,13,16,17-octahydro-(1H,5H,11H,15H-xantheno(2,3,4-ij:5,6,7-i'j')diquinolizin-18-ium, inner salt). Lucifer Yellow IA is disclosed in TABLE 1, and the term Lucifer Yellow is replaced by its known IUPAC name--6-amino-2,3-dihydro-2-(2-((iodoacetyl)amino)ethyl)-1,3-dioxo-1H-benz(de)isoquinoline-5,8-disulfonic acid salt. Cy3 and Cy5 have been replaced by their IUPAC names, 2-(5-(1-(6-(N-(2-maleimdylethyl)-amino)-6-oxohexyl)-1,3-dihydro-3,3-dimethyl-5-sulfo-2H-indol-2-ylidene)-1,3-propyldienyl)-1-ethyl-3,3-dimethyl-5-sulfo-3H-indolium salt, and 2-(5-(1-(6-(N-(2-maleimdylethyl)-amino)-6-oxohexyl)-1,3-dihydro-3,3-dimethyl-5-sulfo-2H-indol-2-ylidene)-1,3-pentadienyl)-1-ethyl-3,3-dimethyl-5-sulfo-3H-indolium salt, respectfully. Dapoxyl® radical has been replaced by its IUPAC name--4-(5-(4-dimethylaminophenyl)oxazole-2-yl)-N (2-bromoacetamidoethyl)sulfonamide. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections of Claims 1-16 for Double Patenting

The Examiner has provisionally rejected Claims 1-16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 and 1-12 of co-pending Application No. 10/039,833 and 10/039,799 respectively. The Examiner asserts that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because both are directed to a biosensor using the same mutated binding protein." Applicants respectfully traverse the rejection.

The subject matter recited in the claims of the instant case is related to biosensors having mutated binding protein and reporter group attached thereto, such that the reporter group provides a detectable and reversible signal change when the mutated binding protein is exposed to varying glucose concentrations, and wherein the detectable and reversible signal change is related to the varying concentrations.

Claims 1-22 of co-pending Application No. 10/039,833 recite elements not recited in the instant claims. Specifically, claims 1-22 of co-pending Application No. 10/039,833 recite a biosensor having mutated binding protein and reporter group attached thereto, and b) an analyte permeable matrix entrapping or encapsulating the mutated binding protein. The instant claims are patentably distinct from co-pending Application No. 10/039,833.

Claims 1-12 of co-pending Application No. 10/039,799 recite elements not recited in the instant claims. Specifically, claims 1-12 of co-pending Application No. 10/039,799 recite a biosensor having mutated binding protein and reporter group attached thereto, *and at least one sensor surface wherein the mutated binding protein is thiol-coupled.* The instant claims are patentably distinct from co-pending Application 2003/0134346.

Reconsideration and withdrawal of the double patenting rejection is requested.

Rejection of Claims 1-5 under 35 USC § 102(e) as being anticipatedby Kratzch et al.

The Examiner has rejected Claims 1-5 under 35 U.S.C. 102(e) as being anticipated by US application 2003/0104595 by Kratzch et al., (Kratzch '595). The Examiner states, "Kratzch et al. teach in paragraph [0008] that glucose biosensors using s-GDH(glucose dehydrogenase) are well known in the art. In paragraphs [0002] + teach the instant invention is to creating an improved s-GDH variant by mutating the binding protein." Applicants respectfully traverse the rejection.

As the Federal Circuit has held, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). *See* MPEP § 2131.

Kratzch '595 fails to teach every element of the claim. Specifcially, Kratzch '595 fails to teach or suggest a reporter group attached to the protein. Kratzch '595 teaches pyrrolpquinoline (PQQ)-dependent, mutant-GDH's. PPQ is a non-covalently bound quinone acting as a co-factor to GDH, which by way of reduction, constitutes the reporter group. (See Example 2, paragraphs

[0102] thru [0112], disclosing the addition of PPQ to agar plates of mutant GDH's). In contrast, Applicants claims 1-5 are explicit in their requirement that reporter group be attached to the binding protein. Accordingly, the claims of the current application are not anticipated by Kratzch '595. Reconsideration and withdrawal of the Examiner's Rejection is respectfully requested.

Rejection of Claims 1-5 under 35 U.S.C. 102 (e) as being anticipated by 6,277,627 to Hellinga, 6,521,446 to Hellinga, and 6,197,534 to Lakowicz

The Examiner has rejected Claims 1-5 under 35 U.S.C. 102(e) as being anticipated by 6,277,627 to Hellinga (Hellinga '627), 6,521,446 to Hellinga (Hellinga '446) and 6,197,534 to Lakowicz et al. (Lakowicz '534). The Examiner states, "[t]hese references all teach use of a mutated protein in combination with a glucose biosensor." Applicants respectfully traverse the rejection.

As discussed above, to anticipate a claim, each and every element of the claimed invention must be taught by the prior art. The cited references, Hellinga '627, Hellinga '446 or Lakowicz '534 fail to teach all of the elements of the claim. Specifically, the references fail to teach that at least one reporter group attached to the protein provides a reversible signal change when the mutated binding protein is exposed to *varying* glucose concentrations. Accordingly, the pending claims of the current application are not anticipated by Hellinga '627 , Hellinga '446 or Lakowicz et al. references. Reconsideration and withdrawal of the Examiner's Rejection is respectfully requested.

Rejection of Claims 1-5 and 11-16 under 35 U.S.C. 102(e) as being anticipated by Marvin et al., Marvin et al., or Tolosa et al.

The Examiner has rejected Claims 1-5 and 11-16 under 35 U.S.C. 102(e) as being anticipated by Marvin et al., *J. Am. Chem. Soc.* (1998) 120:7-11, Marvin et al., *Proc. Natl. Acad. Sci.* (1997) 94:4366-4371, or Tolosa et al., *Anal. Biochem.* (1999) 267:114-120. The Examiner states, "[t]hese references all teach glucose biosensors using a mutated binding protein to quantify glucose using fluorescent measurements." Applicants respectfully traverse the rejection.

Marvin et al. (*J. Am. Chem. Soc.* 1998) teaches single site mutated glucose binding proteins (GGBP) incorporating allosterically and non-allosterically linked fluorescent groups.

Marvin et al. fails to teach a reversable signal change from the reporter group when exposed to varying glucose concentrations. The reference fails to teach all the elements of Applicant's claim.

Marvin et al. (*Proc. Natl. Acad. Sci.* 1997) teaches mutation of maltose binding protein (MBP). Marvin et al. expressly states on page 4369 (last incomplete sentence, continuing on p. 4370), "[t]he mutants do not respond to glucose...and are therefore still specific for maltose." The reference fails to teach all the elements of Applicant's claim.

Tolosa et al., *Anal. Biochem.* (1999) 267:114-120 teach single site mutant GGBP and phase modulated fluorimetry for glucose detection. The reference fails to teach a reversible signal change from the reporter group when exposed to varying glucose concentrations. The reference teaches only titration of protein with glucose (p. 117). The reference fails to teach all the elements of Applicant's claim.

Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 6-10 under 35 U.S.C. 103(a) as being unpatentable over Marvin et al., *J. Am. Chem. Soc.* (1998) 120:7-11, Marvin et al., *Proc. Natl. Acad. Sci.* (1997) 94:4366-4371. or Tolosa et al., *Anal. Biochem.* (1999) 267:114-120

The Examiner has rejected Claims 6-10 under 35 U.S.C. 103(a) as being unpatentable over Marvin et al., *J. Am. Chem. Soc.* (1998) 120:7-11, Marvin et al., *Proc. Natl. Acad. Sci.* (1997) 94:4366-4371 or Tolosa et al., *Anal. Biochem.* (1999) 267:114-120, stating, "[t]hese references all teach glucose biosensors using a mutated binding protein to quantify glucose using fluorescent measurements." The Examiner also relies on *In re Boesch*, and states [i]t would have been within the skill of the art to modify Marvin et al., (J AM Chem. Soc. 1998,120,7 cite by Applicants), Marvin et al. (Proc. Natl. Acad. Sci. cited by Applicant) or Tolosa et al. (Analytical Biochemistry 267,114-120 (1999) cited by Applicants) and modify the amino acids at the claimed positions as optimization of a result effective variable." Applicants respectfully traverse the rejection.

Optimization of a result-effective variable is based on the assumption that the result-effective variable is predictable and already known. Choosing amino acids to modify and the specific mutation positions as being a result effective variable is not predictable or known to provide a particular result. The Circuit Court for Patent Appeals has stated that, while it may

ordinarily be the case that the determination of optimum values for the parameters of a prior art process would be at least prima facie obvious, that conclusion depends upon what the prior art discloses with respect to those parameters. *See In re Sebek*, 465 F.2d 904 (C.C.P.A. 1972). In the teachings of the references it is expressly recited that choice of specific mutation position (or which amino acids) to modify was not reasonably predictable and was not known and thus cannot be previously recognized as result-effective. (For example, see Marvin et al. *J. Am. Chem. Soc* 1988, p. 9, stating: "[s]ince it is impossible to predict which of the residues in the flap region is likely to give the most pronounced allosteric response to ligand binding, we choose to scan the b-sheet portion of the flap and identified four sites for reporter group attachment.") Thus, the choice of amino acid and mutation position as a result effective variable is not one that is predictable and provides well-known results. It follows therefore, the choice of amino acids and mutation positions cannot be relied upon to 'optimize'.

Applicants respectfully request withdrawal and reconsideration of the rejection.

Rejection of Claims 6-16 under 35 U.S.C. 103(a) as being unpatentable over Hellinga (6,277,627), Hellinga (6,521,446) or Lakowicz et al.

The Examiner has rejected Claims 6-16 under 35 U.S.C. 103(a) as being unpatentable over Hellinga '627, Hellinga '446 or Lakowicz '534 stating, "[i]t would have been within the skill of the art to modify Hellinga (6,277,627), Hellinga (6,521,446) or Lakowicz et al. and modify the claimed amino acids at the claimed positions as optimization of a result effective variable." The Examiner also states, "[i]t would have been within the skill of the art to further modify Hellinga (6,277,627), Hellinga (6,521,446) or Lakowicz et al. and use well known fluorescent labels, such as Quantum Red™, Texas Red™, etc., to gain the above advantages and as optimization of a result effective variable." Applicants respectfully traverse the rejection.

As discussed above, the choice of amino acid and mutation positions as a result effective variable is not one that is predictable with well-known results. Likewise, the environment of any attached reporter group in the analyte-bound and analyte-unbound configurations of the protein is not reasonably known and cannot be predicted. The reporter group, either alone or in combination with the specific amino acid substitution and mutation position cannot be a result effective variable. Further, Applicant's choice of amino acid substitutions and reporter group combination provides for more than four fold enhancement of signal (see Table 2). That any

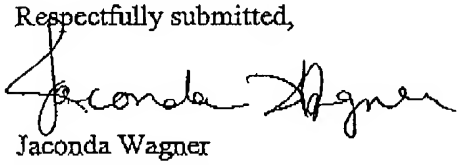
combination of amino acid substitutions in combination with any reporter group would provide substantially improved signal over a single or multiple mutation of the protein and reporter group is an unexpected result. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

Favorable reconsideration of the claims as amended and the remarks presented herein is respectfully requested. Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Jaconda Wagner (Reg. No. 42,207) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-1666 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,



Jaconda Wagner
Attorney for the Applicant(s)
Registration No. 42,207

Becton Dickinson and Company
1 Becton Drive
Franklin Lakes, New Jersey 07417
(201) 847-6659

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